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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,161	09/30/2003	Eric Joel Benjamin	AM101003	5560

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EXAMINER	
HUYNH, CARLIC K	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,161	BENJAMIN ET AL.	
	Examiner	Art Unit	
	Carlic K. Huynh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 35-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :30 September 2003 and 20 April 2003.

DETAILED ACTION

Status of the Claims

1. Claims 1-17 and 35-38 are pending in the application, with claims 18-34 having been cancelled in response to the restriction requirement submitted on October 20, 2006. Accordingly, claims 1-17 and 35-38 are being examined on the merits herein.

Election/Restrictions

2. Applicant's election without traverse of the claims of Group I, namely claims 1-17 and new claims 35-38, in the reply filed on November 2, 2006 is acknowledged.

Claims 18-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on November 2, 2006.

Additionally, Applicant's election without traverse of the species of claim 17, 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide, in the reply filed on November 2, 2006 is acknowledged.

The election/restriction requirement is deemed proper and is made FINAL.

Drawings

3. The drawings are objected to because the label of the Y-axis in **Figure 1** appears twice. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should

include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

4. Claim 17 is objected to because of the following informalities: typographical errors. The compound is "4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]amide". Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claim 15 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,617,333 to Rabindran et al., issued September 9, 2003.

Rabindran et al. disclose an antineoplastic combination comprising a combination of CCI-779 and EKB-569 (4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide) (column 1, lines 13-15).

Rabindran et al., also teach oral formulations including tablets, as well was tablets being made by wet granulation or dry granulation methods, basic excipients including calcium carbonate, and other pharmacologically acceptable excipients (column 7, lines 9-12 and lines 18-30).

Regarding "pH of the composition", as recited in claim 1, pH is an inherent property. Since Rabindran et al. teach a composition that includes 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide and a basic excipient such as calcium carbonate, it is reasonably expected that such a composition would yield a pH of about 8 as recited in claim 1.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 102(e).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-6, 10-11, 16, and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,002,008 to Wissner et al., issued December 14, 1999 in view of Cotton et al. (International Journal of Pharmaceutics 1994, 109, 237-249).

Regarding "basic exicipient" in claims 1-6, 10-11, 16, and 35-38, the basic exicipient is used to stabilize and prevent the degradation of the pharmaceutical composition caused by cyclization of the methylamino-but-2-enoic acid side chain.

Wissner et al. teach a compound of formula (I), namely 4-methylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]amide (column 137, lines 40-41).

Wissner et al. also teach the compounds of the claimed invention may have solid carriers or excipients, including starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose, and kaolin (column 41, lines 46-48).

Furthermore, Wissner et al. teach a solid dosage form (column 41, lines 57-60) and tablets (column 41, lines 10-15).

Wissner et al. do not teach basic excipients in the pharmaceutical composition and concentrations of basic excipients that are sufficient to bring the pH of the composition to at least 8.

Cotton et al. teach that basic excipients, e.g. glycine and sodium carbonate, may be used to stabilize and prevent the degradation of L-649,923, which is caused by the cyclization of its γ-hydroxy free acid. Cotton et al. also teach that an equivalent to 1.0 molar concentration of

glycine brings the pH of the L-649,923 composition to 7.3 and that an equivalent to 0.5 molar concentration of sodium carbonate brings the pH of the L-649,923 composition to 9.5 (Table 6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine 4-methylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]amide and a solid carrier or excipient of Wissner et al. to glycine of Cotton et al. in order to stabilize and prevent the degradation of dimethylamino-but-2-enoic acid side chain caused by its cyclization and to bring the pH of the composition to at least 8.

One of ordinary skill in the art would have been motivated to combine the composition and solid carrier or excipient of Wissner et al. to the basic excipient of Cotton et al. because the basic excipient glycine or sodium carbonate can be used to stabilize and prevent the degradation of acidic groups of compositions and to bring the pH of those compositions to at least 8. Since Cotton et al. teaches that glycine or sodium carbonate can prevent the degradation of L-649,923 caused by the cyclization of its γ-hydroxy free acid, combining Cotton's glycine or sodium carbonate and Wissner's compositions would have reasonably been expected to be effective to stabilize and prevent the degradation of the methylamino-but-2-enoic acid side chain caused by its cyclization and to bring the pH of the composition to at least 8.

Regarding the amounts of the pH of the composition, as recited in claims 4-6 and 37, it is noted that Cotton et al. teach providing glycine and sodium carbonate will yield a composition pH of 7.3 and 9.5, respectively, which closely meets the amounts of pH set forth in claims 4-6 and 37. It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of glycine or sodium carbonate provided in a composition, according to the guidance set forth in Cotton et al., to provide a

composition having desired pH. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

7. Claims 35-38 are also rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,002,008 to Wissner et al., issued December 14, 1999 in view of Cotton et al. (International Journal of Pharmaceutics 1994, 109, 237-249).

Claims 35-38 are still rendered obvious over the teachings of Wissner et al. as product by process claims. Wissner et al. teaches oral formulations and tablets. It is well known that there are a number of processes that will yield tablets including dry granulation and wet granulation. Thus, it would be obvious that tablets are made by processes such as dry granulation or wet granulation. It is noted that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

8. Claims 7-9 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,002,008 to Wissner et al., issued December 14, 1999 in view of Cotton et al. (International Journal of Pharmaceutics 1994, 109, 237-249) as applied to claims 1-6, 10-11, 16, and 35-38 above, and further in view of U.S. Patent No. 5,879,708 to Makino et al., issued March 9, 1999.

Wissner et al. and Cotton et al. are applied as discussed for claims 1-6, 10-11, 16, and 35-38 above, and teach a pharmaceutical composition comprising of a compound of formula (I), a basic excipient, the pH of the composition of at least 8, and an additional pharmaceutically acceptable excipient. Wissner et al. further teaches solid dosage forms and tablets.

Wissner et al. and Cotton et al. do not teach the weight of the basic excipient in relation to the weight of the pharmaceutical composition.

Additionally, Wissner et al. and Cotton et al. do not teach the pharmaceutical composition in sustained release form.

Furthermore, Wissner et al. and Cotton et al. do not teach the pharmaceutical composition as being enteric coated.

Makino et al. teach providing calcium carbonate is 25% of the total weight per tablet of a benzimidazole compound composition (column 13, lines 60-67 and column 14, lines 1-10).

Makino et al. also teach that a benzimidazole compound composition in tablet form may be coated to provide enteric or sustained release property (column 10, lines 30-32).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the composition of Wissner et al. and Cotton et al. to the composition of Makino et al.

One of ordinary skill in the art would have been motivated to combine the composition of Wissner et al. and Cotton et al. to the basic excipient of Makino et al. because the weight of the basic excipient, namely calcium carbonate, of the pharmaceutical composition comprising of a compound of formula (I), namely 4-methylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]amide, would be 25% of the total weight of the composition. Combining

Wissner's and Cotton's compositions with Makino's basic excipient would have reasonably been expected to be effective to make the compound of formula (I), namely 4-methylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]amide, with a basic excipient being 25% of the total weight of the composition.

Furthermore, one of ordinary skill in the art would have been motivated to combine the composition of Wissner et al. and Cotton et al. to the composition of Makino et al. because the pharmaceutical composition of Makino et al. is in tablet form can be coated to provide enteric or sustained release property. Combining Wissner's and Cotton's compositions with Makino's composition would have reasonably been expected to be effective to make the pharmaceutical composition in tablet form, which could then be coated to provide enteric or sustained release property.

Regarding the weights of the basic excipient of the composition, as recited in claims 7-9, it is noted that Makino et al. teaches providing calcium carbonate will yield a weight that is 25% of the total weight of the composition, which closely meets the amounts of basic excipient weight set forth in claims 7-9. It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of calcium carbonate provided in a composition, according to the guidance set forth in Makino et al., to provide a composition having desired basic excipient weight. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

9. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,002,008 to Wissner et al., issued December 14, 1999 in view of Cotton et al. (International Journal of Pharmaceutics 1994, 109, 237-249) as applied to claims 1-6, 10-11, 16, and 35-38 above, and further in view of U.S. Patent Application Publication No. 2003/0198674 to Curatolo et al., published October 23, 2003.

Wissner et al. and Cotton et al. are applied as discussed for claims 1-6, 10-11, 16, and 35-38 above, and teach a pharmaceutical composition comprising of a compound of formula (I), a basic excipient, the pH of the composition of at least 8, and an additional pharmaceutically acceptable excipient. Wissner et al. further teaches solid dosage forms and tablets.

Wissner et al. and Cotton et al. do not teach the composition as an immediate release form.

Curatolo et al. teach providing a quinolin derivative, namely 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-l-carboxylic acid ethyl ester, by an immediate release form (paragraph [0048], for example).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the composition of Wissner et al. and Cotton et al. to an immediate release form of a quinolin derivative of Curatolo et al.

One of ordinary skill in the art would have been motivated to combine the composition of Wissner et al. and Cotton et al. with an immediate release form of a quinolin derivative of Curatolo et al. because the compound of formula (I), namely 4-methylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]amide may be made as an immediate release form. Combining Wissner's and Cotton's compositions with Curatolo's immediate release form

would have reasonably been expected to be effective to make the compound of formula (I), namely 4-methylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]amide, as an immediate release form.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 16-17 and 38 are rejected under 35 U.S.C. 112, 2nd paragraph for having insufficient antecedent basis from the independent claim, claim 1.

Claims 16-17 and 38 recites the limitation of "the compound comprising of 4-dimethylamino-but-2-enoic acid [4-(3-bromo-phenyl-amino)-3-cyano-7-methoxy-quinolin-6-yl]amide, 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenyl-amino)-3-cyano-7-ethoxy-quinolin-6-yl]amide, or 4-dimethylamino-but-2-enoic acid [4-(3-bromo-phenyl-amino)-3-cyano-7-methoxy-quinolin-6-yl]amide" which lacks sufficient antecedent basis from claim 1. The elected species of 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]amide in claims 16-17 and 38 do not meet the limitation of claim 1, from which claims 16-17 and 38 are dependent, because 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide contains a N,N-dialkylaminoalkyl of 1 carbon atom, not a "N,N-dialkylaminoalkyl of 3-12 carbon atoms" as recited in claim 1.

11. Claim 17 is rejected under 35 U.S.C. 112, 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

invention. The phrase "the compound comprises" is indefinite because Applicant has elected the specie of "4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]amide".

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER